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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SOUAYA, JEHANNE E	
ART UNIT	PAPER NUMBER
1655	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/451,291	Chen
Examiner	**Art Unit**
Jehanne Souaya	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 9, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1 and 4-51* is/are pending in the application.

4a) Of the above, claim(s) *6-10, 14-35, and 38-44* is/are withdrawn from consideration.

5) ☒ Claim(s) *4, 5, and 46* is/are allowed.

6) ☒ Claim(s) *1, 11-13, 36, 37, 45, and 47-51* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Currently, claims 1 and 4-51 are pending in the instant application. Claims 6-10, 14-35, and 38-44 have been withdrawn from consideration. Claims 1, 4-5, 11-13, 36-37, and 45-51 are under consideration. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied (necessitated by amendment) or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

Enablement

3. Claims 1, 11-13, 36-37, and 45-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid sequence that encodes a polypeptide with the ability to costimulate a T cell, wherein the polypeptide is an amino acid sequence consisting of SEQ ID NO 1, or SEQ ID NO 3, the complements of such, and vectors and host cells comprising such, does not reasonably provide enablement for a nucleic acid

sequence that encodes a polypeptide with the ability to co-stimulate a T cell wherein the polypeptide consists of SEQ ID NOS 1 or 3 but with one or more conservative substitutions or for a nucleic acid sequence that encodes a polypeptide with the ability to co-stimulate a T cell wherein the nucleic acid is at least 50 nucleotides long and wherein the polypeptide consists of a functional fragment of SEQ ID NO 1 or 3 or functional fragments with one or more conservative substitutions, or to vectors and host cells comprising such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are broadly drawn to nucleic acid sequences which encode substitution mutants of SEQ ID NO 1 or 3, wherein the substitutions are conservative substitutions, to DNA comprising nucleic acid sequences which encode polypeptides with the ability to costimulate a T cell, wherein the nucleic acid sequences are at least 50 nucleotides long and wherein the polypeptide consists of a functional fragment of SEQ ID NOS 1 or 3, or functional fragments of SEQ ID NOS 1 or 3 with one or more conservative substitutions. Thus the claims broadly encompass any functional fragment, allelic variant, or homolog of SEQ ID NOS 1 and 3, from any source, however neither the specification, nor the art enable the skilled artisan to make or use the invention without undue experimentation. It is well established that to claim a chemical compound, such as a polynucleotide, the inventor must be able to define the compound so as to distinguish the compound from other materials. The claimed compound must be defined in terms so as to provide a permanent and definite idea of the complete and operative invention. In

the instant case, the claimed polynucleotides have not been clearly defined in terms of structure and function, and therefore one cannot make and use the polynucleotides as claimed. As stated in Vaek (CAFC 20 USPQ2d 1438, the "specification must teach those of skill in the art how to make and use the invention as broadly as it is claimed." However, in order to be able to make an invention, one must be able to clearly define that invention.

The specification sets forth that the invention is based on the cloning of human and mouse cDNA molecules encoding novel homologous molecules that co-stimulate the T cell response of both species. The specification teaches that using PCR primers with sequences derived from an expressed sequence tag that had "significant" homology to human B7-1 and B7-2, a cDNA sequence that corresponded to an ORF (SEQ ID NO 2) was identified that encoded a novel B7-related molecule (p. 9). The specification teaches that the human polypeptide is designated hB7-H1 (SEQ ID NO 1) and the mouse polypeptide is mB7-H1 (SEQ ID NO 3) (see p. 1 of specification). The specification teaches that translation of the cDNA sequence (SEQ ID NO 2) indicated that the polypeptide (SEQ ID NO 1) it encoded is a type I transmembrane protein of 290 amino acids with contained an immunoglobulin "V-like" domain, Ig "C-like" domain, a transmembrane domain and a 30 amino acid cytoplasmic domain. The specification also teaches, however, that the extracellular domain of hB7-H1 only had 20 % amino acid identity with B7-1 and 15% with B7-2, and that the cytoplasmic domain was highly divergent from that of B7-1 and B7-2.

Therefore, while hB7-H1 appears to be a homolog of B7 related sequences, it is unpredictable from the disclosure in the specification as to which molecules would be functional in costimulating T cells and also satisfy the broad structural requirements to which the claims are drawn. Neither the specification nor the claims set forth any functional characteristics that are specific to hB7-H1 (ie: to particular domains) that a skilled artisan could use to identify polynucleotides that constitute the B7 related polynucleotides of the claimed invention from other B7 related molecules, other than those described by SEQ ID NO. That is, it is unpredictable as to how the skilled artisan could modify the polypeptides of SEQ ID NO 1 or 3 without altering it's biological activity. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence homology results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule and therefore lacks support regarding enablement. (See Russel et al, J. Mol. Biol. Vol. 244, 1994, pp 332-350, who teaches that the results of an analysis of side chain to side chain secondary structure and accessibility between related proteins suggest that there is little in common between distantly related protein structures and that secondary structure lengths and loops in distantly related structures vary substantially- p. 345). Furthermore, Juppner exemplifies the unpredictability as to the effect of even conservative substitutions on functional activity of

proteins. Juppner (Bone; vol. 17, pp 39S-42S; 1995) teaches that despite significant structural conservation between rat and human PTH/PTHrP receptors (share 91% amino acid identity) the receptors have strikingly different affinities for PTH(1-34) analogs that are truncated at the amino terminus (see abstract and p. 39S, col. 2, last para., fig. 1, fig illustrates that a number of conservative substitutions between the rat and the human and the opossum sequences). Juppner teaches that similar functional discrepancies were observed when testing rat and opossum PTH/PTHrP receptors which share 78% amino acid sequence homology. Juppner teaches that while rat recaptor bound hPTH(1-34) and [Arg2]hPTH(1-34)amide ([Arg2]PTH) with similar binding affinity, the opossum receptor showed approximately 35 fold lower binding affinity for [Arg2]PTH when compared with PTH (1-34).

In addition, in teaching the nucleic acid sequences of SEQ ID NOS 2 and 4, and the amino acid sequences of SEQ ID NOS 1 and 3, applicant has not taught the isolation of a representative number of polynucleotides that fall within the scope of the large genus encompassed by the instant claims. Thus, while the teachings of the specification and of the prior art would enable a skilled artisan to make and use polynucleotides that encode a polypeptide consisting of SEQ ID NO: 1 or 3 and *the complement* of SEQ ID NO: 1 or 3, it is unpredictable as to whether a skilled artisan could make and use an isolated DNA comprising any nucleic acid sequence that encodes a polypeptide with the ability to co-stimulate a T cell wherein the polypeptide consists of SEQ ID NOS 1 or 3 but with one or more conservative substitutions or for a nucleic acid sequence that encodes a polypeptide with the ability to co-

stimulate a T cell wherein the nucleic acid is at least 50 nucleotides long and wherein the polypeptide consists of a functional fragment of SEQ ID NO 1 or 3 or functional fragments with one or more conservative substitutions, or to vectors and host cells comprising such. It would require trial and error, the results of which are unpredictable, for a skilled artisan to make and use the invention as broadly as it is claimed. This constitutes undue experimentation.

Response to Arguments

4. The response traverses the rejection. The response assets that using the teaching and guidance of the specification, one of skill in the art would by entirely routine experimentation e able to test whether polypeptides (encoded by the nucleic acids of the invention) containing conservative substitutions of interest retained the ability to co-stimulate a T cell. This argument has been thoroughly reviewed but was found unpersuasive because while the specification teaches experiments to determine co-stimulation of T cells, it is unpredictable as to which conservative substitutions in SEQ ID NOS 1 or 3 the skilled artisan could make and still obtain a polypeptide with the ability to co-stimulate a T cell (see Juppner above). Furthermore, neither the specification nor the claims set forth any structural and functional characteristics that the skilled artisan could use to determine where one could make conservative substitutions that might retain the ability to co-stimulate a T cell or which sequences (ie: particular domains) that would constitute functional fragments of SEQ ID NOS 1 and 3 (let alone conservative substitutions of such) and still retain the ability to costimulate a T cell. Thus the skilled artisan

would be required to use trial and error to make and use the polynucleotides of the claimed invention, the results of which are unpredictable, thus constituting undue experimentation.

Written Description

5. Claims 1, 11-13, 36-37, 45, and 47-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to nucleic acid sequences which encode substitution mutants of SEQ ID NO 1 or 3, wherein the substitutions are conservative substitutions, to DNA comprising nucleic acid sequences which encode polypeptides with the ability to costimulate a T cell, wherein the nucleic acid sequences are at least 50 nucleotides long and wherein the polypeptide consists of a functional fragment of SEQ ID NOS 1 or 3, or functional fragments of SEQ ID NOS 1 or 3 with one or more conservative substitutions. The claims, therefore broadly encompass any functional fragment, allelic variant, or homolog of SEQ ID NO 1 and SEQ ID NO 3, from any source, however the specification has only taught sequences consisting of SEQ ID NOS 2 and 4 (nucleic acid sequences that encode the polypeptides of SEQ ID NOS 1 and 3 respectively). Furthermore, neither the specification nor the claims set forth any structural and functional characteristics that the skilled artisan could use to determine where one could make conservative substitutions that might retain the ability to co-stimulate a T cell or which sequences

(ie: particular domains) that would constitute functional fragments of SEQ ID NOS 1 and 3 (let alone conservative substitutions of such) and still retain the ability to costimulate a T cell. Many sequences are encompassed by applicant's claims. The claimed invention is drawn to a broad genus for which a representative number of sequences for each genus must be disclosed to meet the written description requirement of 112/1st paragraph. As set forth by the Court in *Vas Cath Inc. V. Mahurkar,* 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the claimed invention. There is not adequate description of the genus polynucleotides encompassed by the instant claims. One of skill in the art would conclude that applicant was not in possession of the claimed nucleic acid sequences because the description of SEQ ID NOS 1 and 3 is of only 2 members of the possible nucleic acids that belong to this genus and is not representative of the homologs, variants, mutants and to the genomic sequences that contain these homologs, variants, and mutants to support the claims.

Response to Arguments

6. The response traverses the rejection with the assertion that the amendments have rendered the rejection moot. This argument has been thoroughly reviewed but was deemed unpersuasive for the reasons made of record in paragraph 4 above.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. WO 01/14556 teaches the sequences of the instantly claimed invention.

9. Claims 4 and 5 are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

Jehanne Souaya
Jehanne Souaya
Patent examiner
Art Unit 1655
Dec, 7, 2001